

# Impact of Diabetes Mellitus on the Evaluation of Stable Chest Pain Patients: Insights From the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) Trial

Abhinav Sharma, MD; Nishant K. Sekaran, MD; Adrian Coles, PhD; Neha J. Pagidipati, MD, MPH; Udo Hoffmann, MD; Daniel B. Mark, MD, MPH; Kerry L. Lee, PhD; Hussein R. Al-Khalidi, PhD; Michael T. Lu, MD; Patricia A. Pellikka, MD; Quynh A. Trong, MD, MPH; Pamela S. Douglas, MD

**Background**—The impact of diabetes mellitus on the clinical presentation and noninvasive test (NIT) results among stable outpatients presenting with symptoms suggestive of coronary artery disease (CAD) has not been well described.

**Methods and Results**—The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial enrolled 10 003 patients with known diabetic status, of whom 8966 were tested as randomized and had interpretable NIT results (1908 with diabetes mellitus, 21%). Differences in symptoms and NIT results were evaluated using logistic regression. Patients with diabetes mellitus (versus without) were similar in age (median 61 versus 60 years) and sex (female 54% versus 52%), had a greater burden of cardiovascular comorbidities, and had a similar likelihood of nonchest pain symptoms (29% versus 27%). The Diamond-Forrester/Coronary Artery Surgery Study score predicted that patients with diabetes mellitus (versus without) had similar likelihood of obstructive CAD (low 1.8% versus 2.7%; intermediate 92.3% versus 92.6%; high 5.9% versus 4.7%). Physicians estimated patients with diabetes mellitus to have a higher likelihood of obstructive CAD (low to very low: 28.3% versus 40.1%; intermediate 63.9% versus 55.9%; high to very high 7.8% versus 4.0%). Patients with diabetes mellitus (versus without) were more likely to have a positive NIT result (15% versus 11%; adjusted odds ratio, 1.23;  $P=0.01$ ).

**Conclusions**—Stable chest pain patients with and without diabetes mellitus have similar presentation and pretest likelihood of obstructive CAD; however, physicians perceive that patients with diabetes mellitus have a higher pretest likelihood of obstructive CAD, an assessment supported by increased risk of a positive NIT. Further evaluation of diabetes mellitus's influence on CAD assessment is required.

**Clinical Trial Registration**—URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT01174550. (*J Am Heart Assoc.* 2017;6:e007019. DOI: 10.1161/JAHA.117.007019.)

**Key Words:** coronary artery disease • diabetes mellitus • noninvasive imaging

In the United States, over 29 million adults have a diagnosis of diabetes mellitus, and the prevalence will grow in the next few decades.<sup>1</sup> Although cardiovascular disease is one of the leading causes of death and disability among patients with diabetes mellitus,<sup>2,3</sup> identifying these patients remains a challenge—particularly among the majority of patients who do not present with acute coronary

syndromes.<sup>4–7</sup> Among stable symptomatic outpatients with diabetes mellitus, there are few data regarding patient demographic and presentation profiles, physician practice with respect to noninvasive test (NIT) selection, rates of NIT positivity, and predictors of NIT results, information which is required to improve the value of healthcare services delivered to this at-risk group. We analyzed these questions using

From the Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC (A.S., N.K.S., A.C., N.J.P., D.B.M., K.L.L., H.R.A.-K., P.S.D.); Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada (A.S.); Massachusetts General Hospital, Harvard Medical School, Boston, MA (U.H., M.T.L.); Mayo Clinic, Rochester, MN (P.A.P.); New York-Presbyterian Hospital, Weill Cornell Medicine, New York, NY (Q.A.T.).

Accompanying Tables S1, S2 and Figure S1 are available at <http://jaha.ahajournals.org/content/6/11/e007019/DC1/embed/inline-supplementary-material-1.pdf>

**Correspondence to:** Pamela S. Douglas, MD, Duke University School of Medicine, 7022 North Pavilion DUMC, P.O. Box 17969, Durham, NC 27715. E-mail: [pamela.douglas@duke.edu](mailto:pamela.douglas@duke.edu)

Received June 22, 2017; accepted September 7, 2017.

© 2017 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

## Clinical Perspective

### What Is New?

- Using data from the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, we demonstrated that patients with and without diabetes mellitus have similar clinical presentations.
- Patients with diabetes mellitus are more likely to be referred for stress imaging tests than nonimaging tests and, specifically, nuclear tests.
- Patients with and without diabetes mellitus have a similar pretest likelihood of obstructive coronary artery disease based on the Diamond-Forrester and Coronary Artery Surgery Study scores.
- In contrast, physicians perceive that patients with diabetes mellitus have a higher pretest likelihood of obstructive coronary artery disease, an assessment supported by an increased likelihood of a positive noninvasive test.

### What Are the Clinical Implications?

- The presence of diabetes mellitus influences the diagnostic pathway and results of noninvasive test among low-risk patients with symptoms suggestive of coronary artery disease.
- For patients with diabetes mellitus and stable chest pain symptoms, additional strategies to assess for coronary artery disease, including optimal test selection and risk stratification, need to be evaluated.

contemporary data from the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), a randomized trial of diagnostic evaluation strategy in 10 003 stable outpatients with symptoms suggestive of coronary artery disease (CAD).<sup>8,9</sup> We compared symptomatic patients with and without diabetes mellitus to assess: (1) demographic and risk factor profiles; (2) clinical presentation; (3) physician preference for functional stress test modality; (4) NIT results; and (5) predictors of NIT positivity and the ability of these predictors to discriminate for a positive NIT result.

## Methods

### Patient Population

The methods and results of the PROMISE trial have been previously described.<sup>8,9</sup> In brief, 10 003 symptomatic stable outpatients without a history of CAD were randomized to initial anatomical testing with 64-slice multi-detector coronary computed tomographic angiography or functional testing (exercise ECG, stress nuclear imaging, or stress echocardiogram). There were 2144 patients with diabetes mellitus (21%) and 7858 without diabetes mellitus (79%); diabetic status of 1

patient was unknown. Before randomization, the local providers were required to prespecify the functional test that the patient would undergo should the patient be randomized to that arm. Local or central institutional review boards approved the study at the coordinating centers and each of the 193 enrolling sites in North America. Patients provided written informed consent before randomization.

### Baseline Variable and Data Collection

Baseline patient data on demographics, risk factor profiles, ECG findings, symptoms, and CAD risk estimates were collected for all patients. Data from risk assessment scores (2008 Framingham score,<sup>10</sup> the 2013 Atherosclerotic Cardiovascular Disease [ASCVD] score,<sup>11</sup> and the 2012 combined Diamond-Forrester and CASS [Coronary Artery Surgery Study] score<sup>12</sup>) were calculated for the entire population. In calculating the Framingham and ASCVD scores, the single imputation method was used to replace missing values of cholesterol and high-density lipoprotein with the mean of nonmissing observations, as described previously.<sup>13,14</sup> In particular, the imputation of cholesterol was stratified by history of dyslipidemia and statin use at baseline, and the imputation of high-density lipoprotein was stratified by sex. Test results according to site interpretation were recorded for the first NIT performed. Overall, there were 8966 patients with an interpretable NIT (1908 [21%] with diabetes mellitus and 7058 [79%] without diabetes mellitus). On the coronary computed tomography angiography scan, positivity was defined as  $\geq 70\%$  major epicardial stenosis or  $\geq 50\%$  left main stenosis. Positivity on an exercise ECG was defined as ST-segment changes consistent with ischemia during stress being detected or if the test was terminated early ( $< 3$  minutes) because of reproduction of symptoms, arrhythmia, and/or hypotension. Positivity on stress nuclear and stress echocardiography tests was defined as inducible ischemia in at least 1 coronary territory (septal/anterior/apical; inferior/posterior; or lateral).

### Statistical Analysis

Baseline characteristics were summarized using median (25th, 75th percentiles) for continuous variables and frequencies/percentages for categorical variables.

To determine whether the likelihood of a physician preferring an imaging functional test over a nonimaging functional test differed between diabetic and nondiabetic patients, a multivariable generalized linear mixed model was fit using a generalized logit-link function. To determine whether this relationship persisted after accounting for demographic information, the model was adjusted for age, sex, and testing site (as a random effect). A similar approach was utilized to assess whether the likelihood of a physician

preferring stress nuclear over stress echocardiography differed between diabetic and nondiabetic patients who received an imaging stress test.

To assess whether the likelihood of having a positive NIT differed between patients with and without diabetes mellitus, a logistic regression model was fit. Adjusted analyses controlled for randomized testing modality, age, and sex.

To determine the factors most predictive of a positive NIT in patients with or without diabetes mellitus separately, multivariable logistic regression models were fit using step-wise variable selection with liberal entry and exit criteria (entry,  $P < 0.1$ ; exit,  $P > 0.2$ ) to select the best subset of predictors from among a comprehensive set of clinically guided candidate predictors. The following candidate predictors were considered for patients with or without diabetes mellitus: age; race; body mass index; hypertension; sex; metabolic syndrome; dyslipidemia; history of carotid, peripheral vascular, or cerebrovascular disease; history of heart failure; smoking (ever, never); family history of premature CAD; depression; physical activity; CAD equivalent; Framingham Risk Score (2008); ASCVD risk prediction; Diamond-Forrester; Combined Diamond-Forrester and CASS; Diamond-Forrester (2011); presenting symptom; and chest pain characterization. In each case, age, sex, and chest pain characterization were forced into the final selected model. Calibration of the final models selected was assessed using the Hosmer–Lemeshow goodness-of-fit test, and discrimination was assessed using the area under a receiver operating characteristic curve.

All statistical calculations were conducted using SAS (version 9.4; SAS Institute Inc, Cary, NC).

## Results

### Baseline Demographics and Primary Presenting Symptoms

Patient distribution and study design are shown in Figure S1. Among all enrolled patients ( $n=10\,002$ ), there were no clinically significant differences between patients with diabetes mellitus ( $n=2144$ ) and those without diabetes mellitus ( $n=7858$ ) with regard to age (median 61 versus 60 years) or sex (female 54% versus 52%). However, patients with diabetes mellitus were more likely to have hypertension (80% versus 61%), dyslipidemia (77% versus 65%), depression (24% versus 20%), and a sedentary lifestyle (57% versus 47%; Table 1). Patients with diabetes mellitus had a higher body mass index (33 versus 29 kg/m<sup>2</sup>) and were more likely to have metabolic syndrome (85% versus 25%; Table 1). Patients with diabetes mellitus, compared with those without, were more likely to be on aspirin, statin, beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, or diuretics (Table 1). At baseline, 74% of patients with diabetes mellitus

were on oral hypoglycemics, and 23% were on insulin, with the remainder treated with diet alone.

Chest pain was the most common presenting symptom among patients with and without diabetes mellitus (Table 1). There was no difference in the characteristics of the chest pain (ie, “aching/dull,” “burning/pins and needles,” or “crushing/pressure/squeezing/tightness”) between patients with and without diabetes mellitus. Patients with diabetes mellitus were only slightly more likely to present with primary nonchest pain symptoms compared with those without diabetes mellitus (29% versus 27%), and dyspnea was more frequent (18% versus 14%). Site physicians were more likely to rate the chest pain among patients with diabetes mellitus as being typical (14% versus 11%).

### Risk Scores and Coronary Disease Likelihood

The predicted risks of cardiovascular events were higher for patients with diabetes mellitus compared with those without diabetes mellitus for the Framingham<sup>10</sup> and ASCVD<sup>11</sup> risk scores (Table 2). The median pretest likelihood of obstructive CAD was similar for patients with diabetes mellitus as measured by the combined Diamond-Forrester and CASS<sup>12</sup> (Table 2). Site physicians estimated that patients with diabetes mellitus were less likely to have “very low” and “low” pretest likelihood of obstructive CAD; conversely, physicians estimated that patients with diabetes mellitus were more likely to have “intermediate,” “high,” and “very high” pretest likelihood of obstructive CAD.

### Test Preferences

Before randomization, providers were asked their functional test preference for each patient. Compared with patients without diabetes mellitus, for those with diabetes mellitus, exercise ECG (7% versus 11%;  $P < 0.001$ ) and stress echocardiography (19% versus 23%;  $P < 0.001$ ) were less frequently specified whereas stress nuclear was more likely (74% versus 66%;  $P < 0.001$ ; Figure 1). Even after multivariable adjustment, patients with diabetes mellitus were more likely to have an imaging versus nonimaging test preferred (93% versus 89%; adjusted odds ratio, 1.90;  $P < 0.001$ ; Table 3). Among those for whom an imaging test was preferred, stress nuclear was specified over stress echocardiography in both patients with and without diabetes mellitus, although the preference was stronger in those with diabetes mellitus (79% versus 74%; adjusted odds ratio, 1.50;  $P < 0.001$ ; Table 3).

### Test Results

Among the 8966 patients who received their initial NIT and had interpretable results (1908 [21%] with diabetes mellitus

**Table 1.** Patient Characteristics

Characteristic	Diabetes Mellitus (N=2144)	No Diabetes Mellitus (N=7858)
<b>Demographics</b>		
Age, y		
Median (25th, 75th)	60.6 (55.0, 66.3)	59.8 (54.3, 65.8)
Female sex, n/N (%)	1151/2144 (53.7)	4119/7858 (52.4)
Race, n/N (%)		
Multiracial	19/2113 (0.9)	76/7802 (1.0)
White	1629/2113 (77.1)	6741/7802 (86.4)
Black	354/2113 (16.8)	742/7802 (9.5)
Asian	75/2113 (3.5)	178/7802 (2.3)
Indian	30/2113 (1.4)	41/7802 (0.5)
Hawaiian	6/2113 (0.3)	24/7802 (0.3)
Ethnicity, n/N (%)		
Hispanic or Latino	256/2132 (12.0)	511/7812 (6.5)
Not Hispanic or Latino	1876/2132 (88.0)	7301/7812 (93.5)
<b>Cardiac risk factors</b>		
BMI (kg/m <sup>2</sup> )		
N	2117	7790
Median (25th, 75th)	32.8 (29.0, 37.4)	28.9 (25.8, 32.9)
Hypertension, n/N (%)	1712/2144 (79.9)	4789/7858 (60.9)
Dyslipidemia, n/N (%)	1656/2144 (77.2)	5111/7858 (65.0)
Smoker (ever/never), n/N (%)	1056/2144 (49.3)	4048/7856 (51.5)
Family history of premature CAD, n/N (%)	655/2140 (30.6)	2547/7830 (32.5)
Depression, n/N (%)	516/2142 (24.1)	1542/7858 (19.6)
Sedentary lifestyle, n/N (%)	1216/2142 (56.8)	3650/7840 (46.6)
Peripheral arterial disease or cerebrovascular disease, n/N (%)	165/2144 (7.7)	387/7857 (4.9)
Metabolic syndrome, n/N (%)	1822/2144 (85.0)	1950/7858 (24.8)
CAD risk equivalent, n/N (%)	2144/2144 (100.0)	387/7858 (4.9)
<b>All primary presenting symptoms, n/N (%)</b>		
Arm or shoulder pain	55/2144 (2.6)	202/7852 (2.6)
Back pain	14/2144 (0.7)	70/7852 (0.9)
Chest pain*	1518/2144 (70.8)	5754/7852 (73.3)
Aching/dull	368/1518 (24.2)	1471/5754 (25.6)
Burning/pins and needles	138/1518 (9.1)	532/5754 (9.2)
Crushing/pressure/squeezing/tightness	746/1518 (49.1)	2854/5754 (49.6)
Other	461/1518 (30.4)	1738/5754 (30.2)
Fatigue or weakness	58/2144 (2.7)	219/7852 (2.8)
Neck or jaw pain	14/2144 (0.7)	95/7852 (1.2)
Palpitations	50/2144 (2.3)	186/7852 (2.4)
Dyspnea	375/2144 (17.5)	1115/7852 (14.2)
Other <sup>†</sup>	60/2144 (2.8)	211/7852 (2.7)

Continued

Table 1. Continued

Characteristic	Diabetes Mellitus (N=2144)	No Diabetes Mellitus (N=7858)
Physician characterization of chest pain, n/N (%)		
Chest pain typicality		
Typical	296/2144 (13.8)	870/7858 (11.1)
Atypical	1653/2144 (77.1)	6119/7858 (77.9)
Noncardiac	195/2144 (9.1)	869/7858 (11.1)
Medication use, n/N (%)		
Aspirin	1098/2118 (51.8)	3181/7450 (42.7)
Statin	1291/2118 (61.0)	3097/7450 (41.6)
Beta-blocker	619/2118 (29.2)	1780/7450 (23.9)
ACEi or ARB	1444/2118 (68.2)	2750/7450 (36.9)
Diuretics	779/2118 (36.8)	1875/7450 (25.2)
Oral hypoglycemic <sup>‡</sup>	1595/2144 (74.4)	0/7858 (0.0)
Insulin <sup>‡</sup>	483/2144 (22.5)	0/7858 (0.0)
ECG findings, n/N (%)		
ECG Q waves	126/2125 (5.9)	328/7784 (4.2)
ECG findings that could interfere with exercise stress test interpretation	147/2126 (6.9)	439/7784 (5.6)
LBBB	27/147 (18.4)	114/439 (26.0)
ST depression	31/147 (21.1)	94/439 (21.4)
LVH with repolarization	25/147 (17.0)	54/439 (12.3)

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; LBBB, left bundle branch block; LVH, left ventricular hypertrophy.

\*“Chest pain—substernal or left anterior” or “Chest pain other” are selected as primary symptoms. Multiple characterizations are possible.

<sup>†</sup>Includes “Diaphoresis/sweating,” “Dizziness/lightheaded,” “Epigastric/abdominal pain,” “Nausea/vomiting,” “Syncope,” and Other.

<sup>‡</sup>Data available only for patients with diabetes mellitus.

and 7058 [79%] without diabetes mellitus), 15% of patients with diabetes mellitus had positive NIT results compared with 11% without diabetes mellitus (unadjusted odds ratio, 1.38;  $P<0.001$ ; adjusted odds ratio, 1.23;  $P=0.010$ ; Table 4). Test positivity by testing modality is described in Figure 2. The distribution of abnormal test results are described in Table S1. Among those patients who underwent computed tomography angiography, 15% of patients with diabetes mellitus had positive test results compared with 11% of those without diabetes mellitus. Among those who underwent stress testing, 15% of patients with diabetes mellitus had positive test results compared with 11% of those without diabetes mellitus. NIT type did not modify the relationship between diabetic status and test positivity (age- and sex-adjusted interaction,  $P=0.93$ ). Among patients with and without diabetes mellitus, the risk of adverse outcomes is greater among patients with a positive NIT result compared with those with a negative NIT result (Table S2). The presence of diabetes mellitus did not modify the relationship between NIT result and death/myocardial infarction/unstable angina hospitalization (adjusted interaction  $P=0.179$ ) or

cardiovascular death/myocardial infarction (adjusted interaction  $P=0.889$ ).

### Predictors of a Positive NIT

The clinical and demographic factors that were most predictive of a positive stress test were determined separately for patients with and without diabetes mellitus (Table 5). Age, sex, and chest pain characteristics were forced into both models. Among patients with diabetes mellitus, nonwhite race and Framingham Risk Score provided additional predictive information, whereas among those without diabetes mellitus, body mass index and sedentary lifestyle provided additional prognostic information. The final areas under the curve of the models were modest at 0.64 for both patients with and without diabetes mellitus.

### Discussion

Cardiovascular disease is the leading cause of death among patients with diabetes mellitus; however, the impact of diabetes mellitus on the clinical presentation, diagnostic evaluation, and

**Table 2.** Risk Scores and Assessment of Coronary Artery Disease Likelihood

Characteristic	Diabetes Mellitus (N=2144)	No Diabetes Mellitus (N=7858)
10-y CVD risk		
Framingham risk score (2008)		
N	2142	7846
Median (25th, 75th)	28.5 (18.8, 42.8)	14.7 (9.4, 24.4)
Low risk (<10%), n/N (%)	82/2142 (3.8)	2174/7846 (27.7)
Intermediate risk (10–20%), n/N (%)	534/2142 (24.9)	3010/7846 (38.4)
High risk (>20%), n/N (%)	1526/2142 (71.2)	2662/7846 (33.9)
ASCVD (2013)		
N	2111	7790
Median (25th, 75th)	19.8 (11.7, 32.4)	9.7 (5.5, 16.6)
Low risk (<7.5%), n/N (%)	230/2111 (10.9)	2974/7790 (38.2)
Elevated risk (>7.5%), n/N (%)	1881/2111 (89.1)	4816/7790 (61.8)
Pretest likelihood of obstructive CAD		
Combined Diamond-Forrester and CASS (2012)		
N	2144	7858
Median (25th, 75th)	51.0 (31.0, 72.0)	51.0 (31.0, 72.0)
Low risk (<10%), n/N (%)	39/2144 (1.8)	211/7858 (2.7)
Intermediate risk (10–90%), n/N (%)	1978/2144 (92.3)	7279/7858 (92.6)
High risk (>90%), n/N (%)	127/2144 (5.9)	368/7858 (4.7)
Physician's estimation of likelihood of significant CAD, n/N (%)*		
Very low (<10%)	95/2141 (4.4)	540/7845 (6.9)
Low (10–30%)	510/2141 (23.8)	2610/7845 (33.3)
Intermediate (31–70%)	1368/2141 (63.9)	4382/7845 (55.9)
High (71–90%)	155/2141 (7.2)	293/7845 (3.7)
Very high (>90%)	13/2141 (0.6)	20/7845 (0.3)

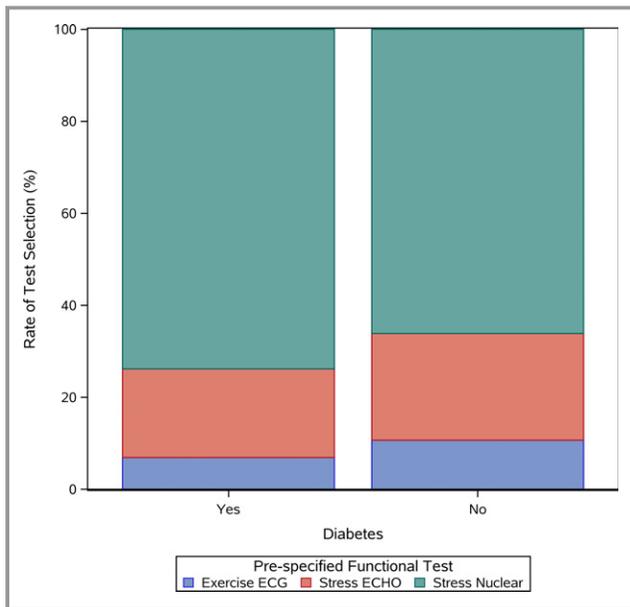
ASCVD indicates Atherosclerotic Cardiovascular Disease; CAD, coronary artery disease; CASS, Coronary Artery Surgery Score; CVD, cardiovascular disease.

\*Provider's assessment of the likelihood that subject has significant epicardial coronary stenosis or left main stenosis. Significant refers to  $\geq 70\%$  epicardial coronary stenosis or  $\geq 50\%$  left main stenosis.

NIT results among stable outpatients presenting with symptoms suggestive of CAD has not been well described. In our analysis of the PROMISE trial, we identified the following major findings: (1) There were significant differences between patients with and without diabetes mellitus in comorbidities and cardiovascular risk, but clinical presentation was similar; (2) patients with and without diabetes mellitus had similar pretest likelihood of obstructive CAD, but physicians perceived patients with diabetes mellitus to have increased likelihood for obstructive CAD; (3) patients with diabetes mellitus were more likely to be referred for stress imaging tests compared with those without diabetes mellitus; (4) while patients with diabetes mellitus were more likely to have a positive NIT result, the absolute increase in risk was modest; and (5) predictors of a positive NIT result differ between patients with and without diabetes mellitus, but the ability to discriminate for a positive NIT result was moderate in both groups.

Our study demonstrated that among stable patients with symptoms suggestive of CAD, patients with diabetes mellitus have a larger burden of cardiovascular risk factors such as obesity, hypertension, and hypercholesterolemia. These results align with other cohort studies of patients with diabetes mellitus and suspected CAD undergoing stress testing.<sup>15,16</sup> Our study also identified that patients with diabetes mellitus had a higher likelihood of emerging risk factors, such as depression, a finding reported in other nonchest pain cohorts.<sup>17</sup> The increased burden of cardiovascular risk factors is reflected in the higher cardiovascular event risk scores in patients with diabetes mellitus compared with those without diabetes mellitus (Table 2).

Our study is one of the largest assessments of the impact of diabetes mellitus on the presentation of low- to intermediate-risk patients for symptoms suggestive of CAD. Most studies evaluating the presentation of CAD in patients with



**Figure 1.** Distribution of functional test preselection. ECHO indicates echocardiogram.

diabetes mellitus have focused on those presenting with acute coronary syndromes,<sup>4–7</sup> with some studies indicating that patients with diabetes mellitus present with atypical symptoms, whereas others do not.<sup>6,18,19</sup> In a study of 4028 patients in Sweden presenting with their first myocardial infarction, diabetes mellitus was not an independent predictor of atypical symptoms, and there were no differences in the characteristics of symptoms between patients with and without diabetes mellitus.<sup>19</sup> However, as highlighted by a previous study on sex differences in clinical presentation, symptoms in an acute setting may not necessarily be extrapolated to the stable outpatient setting.<sup>14</sup> One large cohort study of 8662 ambulatory patients with suspected angina (906 with diabetes mellitus) identified that patients with diabetes mellitus had a 2-fold increase in atypical symptoms of angina (defined as fewer than 2 of the following: constricting quality, central or left-side location,  $\leq 15$  minutes duration, and provocation by exercise).<sup>20</sup> Our analysis

identified that in stable outpatients with symptoms suggestive of CAD, those with and without diabetes mellitus had very similar clinical presentations. Although patients with diabetes mellitus may have differences in clinical presentation that arise from neuropathy or comorbidities, such as obesity, this was not reflected in our study population of stable patients with symptoms suggestive of CAD.

Our study is one of the first to evaluate the impact of diabetes mellitus on the evaluation and testing of stable outpatients with symptoms suggestive of CAD. Overall, our results highlight that diabetes mellitus significantly influences the diagnostic pathway for suspected CAD. ECG exercise stress testing has been reported to have similar sensitivity and specificity among patients with and without diabetes mellitus.<sup>21–23</sup> However, imaging stress tests have greater sensitivity compared with an exercise ECG test,<sup>24,25</sup> leading to calls to preferentially select imaging stress tests in diabetic patients,<sup>26</sup> a decision which may also be influenced by physicians' greater estimated risk of CAD in patients with diabetes mellitus (Table 3). Patients with diabetes mellitus may have decreased ability to exercise, as reflected by higher prevalences of peripheral arterial disease, neuropathy, and obesity, which may have influenced physician stress testing preference. Furthermore, physician perception of increased pretest likelihood of obstructive CAD among patients with diabetes mellitus may have influenced test selection. In addition, the greater likelihood of abnormalities on the baseline ECG (such as Q waves or left bundle branch block) among patients with diabetes mellitus may have also influenced physicians to choose alternative NIT modalities. In our study, physicians were more likely to select stress nuclear over stress echocardiogram. This preference was stronger in patients with diabetes mellitus compared with those without diabetes mellitus despite limited studies in this patient population to guide testing choices. For both stress echocardiography and nuclear stress imaging, limited data suggest that the sensitivity and specificity for CAD detection among patients with and without diabetes mellitus are similar.<sup>24,26–28</sup> To date, there has been no head-to-head comparison in patients with diabetes mellitus assessing the

**Table 3.** Association Between Diabetes Mellitus and Prespecified Choice of Functional Test Category

Diabetes Mellitus n/N (%)	No Diabetes Mellitus n/N (%)	Unadjusted OR (95% CI); P Value	Adjusted OR (95% CI); P Value*
Selection of imaging noninvasive test			
1996/2144 (93)	7020/7858 (89)	1.91 (1.51–2.41); <0.001	1.90 (1.50–2.41); <0.001
Selection of a nuclear stress test (vs stress echo) in those for whom an imaging test was selected			
1583/1996 (79)	5197/7020 (74)	1.51 (1.29–1.77); <0.001	1.50 (1.28–1.75); <0.001

CI indicates confidence interval; OR, odds ratio.

\*Adjusted model controls for age, sex, and testing site (random).

**Table 4.** Association Between Diabetes Mellitus and Positive Initial Noninvasive Test Results

Diabetes Mellitus n/N (%)	No Diabetes Mellitus n/N (%)	Unadjusted OR (95% CI); <i>P</i> Value	Adjusted OR (95% CI); <i>P</i> Value*
289/1908 (15)	809/7058 (11)	1.38 (1.19–1.59); <0.001	1.38 (1.19–1.60); <0.001

CI indicates confidence interval; OR, odds ratio.

\*Adjusted model controls for age, sex, and noninvasive testing modality.

accuracy of stress nuclear versus stress echocardiography to guide NIT selection.

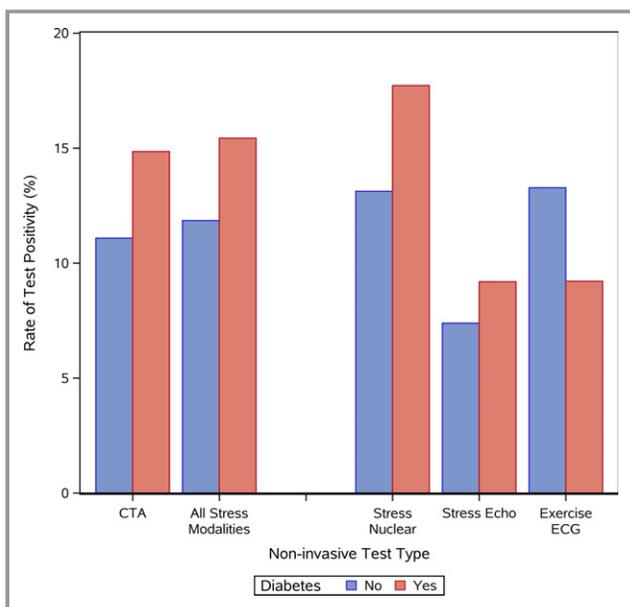
To our knowledge, our study has documented, for the first time, that in stable outpatients with symptoms of CAD, patients with diabetes mellitus, compared with patients without diabetes mellitus, have a greater risk of a positive NIT. Previous studies have demonstrated similar rates of test positivity between patients with and without diabetes mellitus for exercise stress ECG,<sup>21</sup> stress nuclear,<sup>24</sup> and conflicting results for stress echocardiography.<sup>16,28</sup> The differences in our results may reflect differences in patient selection (previous studies were primarily convenience samples), patient demographics, and risk-factor profiles. Although the formal pretest scores suggest that patients with and without diabetes mellitus have similar risk of obstructive CAD, physicians perceive patients with diabetes mellitus to be at higher risk of obstructive CAD. This is supported by the observed increased risk of a positive NIT result. Given that diabetes mellitus is an established cardiovascular risk factor, further studies on the impact of diabetes mellitus on the assessment of CAD is required.

The risk factors that predicted a positive stress test among patients with and without diabetes mellitus were partially

overlapping, with race, typicality of chest pain, demographics, and lifestyle variables included for both patient groups. Among patients with diabetes mellitus, body mass index and sedentary lifestyle do not add any significant predictive information. Among patients without diabetes mellitus, these 2 risk factors are significant. Other demographic and presentation characteristics, such as race and typicality of chest pain, have differential predictive value among patients with and without diabetes mellitus. These results suggest that different factors may be present in the underlying pathogenesis of CAD among patients with and without diabetes mellitus. However, the ability to discriminate for a positive test was modest in both patients with and without diabetes mellitus as reflected by the *c*-statistic. These results suggest that other markers beyond baseline clinical and demographic variables should be evaluated to improve discrimination for a positive NIT among patients with and without diabetes mellitus.

### Strength and Limitations

The PROMISE trial enrolled the largest contemporary cohort of low- to moderate-risk patients presenting with stable symptoms of CAD studied to date. The pragmatic nature of the trial inclusion criteria and its community setting provided a unique opportunity to evaluate real-world differences between patients with and without diabetes mellitus. Our study is a post-hoc study and is subject to the inherent limitations, although analysis by diabetic status was prespecified. However, it is possible that some sites may have preferentially included or excluded diabetic patients, or those with more atypical symptoms, thereby introducing some selection bias. The presence of diabetes mellitus was established by: (1) site investigator-reported history of diabetes mellitus; and (2) the use of antidiabetic drugs. There was no formal testing to confirm the presence of diabetes mellitus. Data on the type, duration, and degree of control of diabetes mellitus were not available. Our use of imputation of missing data for cholesterol and high-density lipoprotein has the potential limitations of distorting the distribution of the variable with missingness as well as its association with other variables, but allowed calculation of Framingham and ASCVD risk scores. The multivariable models evaluating the association of presentation characteristics with NIT positivity were



**Figure 2.** Test positivity by testing modality. CTA indicates computed tomographic angiography; Echo, echocardiogram.

**Table 5.** Predictors of Test Positivity in Patients With and Without Diabetes Mellitus

Important Predictors	Models of Test Positivity* OR (95% CI)	
	Diabetes Mellitus†	No Diabetes Mellitus‡
Age	1.02 (1.00–1.04)	1.03 (1.02–1.05)
Female	0.74 (0.53–1.03)	0.67 (0.55–0.82)
Atypical chest pain	1.09 (0.68–1.73)	1.20 (0.92–1.56)
Typical chest pain	1.43 (0.83–2.48)	1.65 (1.21–2.27)
Race: nonwhite	0.52 (0.36–0.75)	...
Depression	0.74 (0.53–1.03)	...
Presenting symptom: dyspnea	...	0.82 (0.66–1.02)
Body mass index	...	1.01 (1.00–1.03)
Sedentary lifestyle	...	1.17 (1.00–1.36)
Framingham Risk Score (2008)	1.01 (1.00–1.02)	1.02 (1.01–1.02)

CI indicates confidence interval; OR, odds ratio.

\*Final models for patients with or without diabetes mellitus selected using step-wise selection (entry criterion:  $P < 0.1$ ; exit criterion:  $P > 0.2$ ) from the following candidate predictors: age; race; body mass index; hypertension; sex; metabolic syndrome; dyslipidemia; history of carotid, peripheral vascular, or cerebrovascular disease; history of heart failure; smoking (ever, never); family history of premature coronary artery disease (CAD); depression; physical activity; CAD equivalent; Framingham Risk Score (2008); Atherosclerotic Cardiovascular Disease risk prediction; Diamond-Forrester; Combined Diamond-Forrester and Coronary Artery Surgery Score; Diamond-Forrester (2011); presenting symptom; and chest pain characterization. Age, sex, and chest pain characterization forced into each model.

†The final model for patients with diabetes mellitus was well calibrated (Hosmer–Lemeshow Goodness of Fit  $P$  value, 0.345) and had good discriminatory capacity (area under the curve, 0.64 [95% CI, 0.60–0.67]).

‡The final model for patients without diabetes mellitus was well calibrated (Hosmer–Lemeshow Goodness of Fit  $P$  value, 0.234) and had good discriminatory capacity (area under the curve, 0.64 [95% CI, 0.62–0.66]).

exploratory, but have been used in a previous analysis of the PROMISE trial.<sup>14</sup>

## Conclusions

Diabetes mellitus significantly affects clinical presentation, risk-factor profile, stress test selection, NIT results, and predictors of a positive NIT among low-risk patients with symptoms suggestive of coronary artery disease. However, among patients with diabetes mellitus, typical chest pain is the most common presenting complaint, and clinical presentation is similar compared with patients without diabetes mellitus. Patients with diabetes mellitus are more likely to be referred for stress imaging tests than nonimaging test and, specifically, nuclear tests. Furthermore, physicians estimate that patients with diabetes mellitus have a higher risk of obstructive CAD, and this assessment is supported by the increased risk of a positive NIT observed in our study. Given that diabetes mellitus is an established cardiovascular risk

factor, additional strategies to assess for coronary artery disease, including optimal test selection and risk stratification, need to be evaluated for patients with diabetes mellitus and stable chest pain symptoms.

## Sources of Funding

This project was supported by grants R01HL098237, R01HL098236, R01HL98305, and R01HL098235 from the National Heart, Lung, and Blood Institute (NHLBI). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the article, and its final contents. This article does not necessarily represent the official views of the NHLBI.

## Disclosures

Sharma reports receiving support from Bayer-Canadian Cardiovascular Society, Alberta Innovates Health Solution, Roche Diagnostics, and Takeda. Pagidipati reports having ownership in Freedom Health, Inc; Physician Partners, LLC; RXAdvance, LLC; and Florida Medical Associates, LLC. Hoffmann reports receiving grants from HeartFlow and Kowa Pharmaceuticals. Mark reports receiving grants from the National Institutes of Health, Eli Lilly and Company, Bristol-Myers Squibb, Gilead Sciences, AGA Medical Corporation, Merck & Company, Oxygen Therapeutics, and AstraZeneca and personal fees from CardioDx, Medtronic, and St. Jude Medical. Lu reports receiving an American Roentgen Ray Society Scholarship. Lee reports receiving grants from the National Institutes of Health. Trong reports receiving grant support from Qi Imaging LLC, and consulting fees from the American College of Radiology, Society of Cardiovascular Computed Tomography, Aralez Pharmaceuticals, and HeartFlow. Douglas reports receiving grant support from HeartFlow and service on a data and safety monitoring board for GE HealthCare.

## References

- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation*. 2016;133:e38–e360.
- Schramm TK, Gislason GH, Kober L, Rasmussen S, Rasmussen JN, Abildstrøm SZ, Hansen ML, Folke F, Buch P, Madsen M, Vaag A, Torp-Pedersen C. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. *Circulation*. 2008;117:1945–1954.
- Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229–234.

4. Canto JG, Shlipak MG, Rogers WJ, Malmgren JA, Frederick PD, Lambrew CT, Ornato JP, Barron HV, Kiefe CI. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. *JAMA*. 2000;283:3223–3229.
5. Čulić V, Eterović D, Mirić D, Silić N. Symptom presentation of acute myocardial infarction: influence of sex, age, and risk factors. *Am Heart J*. 2002;144:1012–1017.
6. Khafaji HA, Suwaidi JM. Atypical presentation of acute and chronic coronary artery disease in diabetics. *World J Cardiol*. 2014;6:802–813.
7. Goldberg RJ, Goff D, Cooper L, Luepker R, Zapka J, Bittner V, Osganian S, Lessard D, Cornell C, Meshack A, Mann C, Gilliland J, Feldman H. Age and sex differences in presentation of symptoms among patients with acute coronary disease: the REACT trial. *Coron Artery Dis*. 2000;11:399–407.
8. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med*. 2015;372:1291–1300.
9. Douglas PS, Hoffmann U, Lee KL, Mark DB, Al-Khalidi HR, Anstrom K, Dolor RJ, Kosinski A, Krucoff MW, Mudrick DW, Patel MR, Picard MH, Udelson JE, Velazquez EJ, Cooper L; PROMISE Investigators. PROspective Multicenter Imaging Study for Evaluation of chest pain: rationale and design of the PROMISE trial. *Am Heart J*. 2014;167:796–803.e1.
10. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.
11. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2935–2959.
12. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB III, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–e164.
13. Pagidipati NJ, Hemal K, Coles A, Mark DB, Dolor RJ, Pellikka PA, Hoffmann U, Litwin SE, Udelson J, Daubert MA, Shah SH, Martinez B, Lee KL, Douglas PS. Sex differences in functional and CT angiography testing in patients with suspected coronary artery disease. *J Am Coll Cardiol*. 2016;67:2607–2616.
14. Hemal K, Pagidipati NJ, Coles A, Dolor RJ, Mark DB, Pellikka PA, Hoffmann U, Litwin SE, Daubert MA, Shah SH, Ariani K, Bullock-Palmer RP, Martinez B, Lee KL, Douglas PS. Sex differences in demographics, risk factors, presentation, and noninvasive testing in stable outpatients with suspected coronary artery disease: insights from the PROMISE trial. *JACC Cardiovasc Imaging*. 2016;9:337–346.
15. Cortigiani L, Sicari R, Desideri A, Bigi R, Bovenzi F, Picano E; VIDA (Viability Identification with Dobutamine Administration) Study Group. Dobutamine stress echocardiography and the effect of revascularization on outcome in diabetic and non-diabetic patients with chronic ischaemic left ventricular dysfunction. *Eur J Heart Fail*. 2007;9:1038–1043.
16. Cortigiani L, Borelli L, Raciti M, Bovenzi F, Picano E, Molinaro S, Sicari R. Prediction of mortality by stress echocardiography in 2835 diabetic and 11 305 nondiabetic patients. *Circ Cardiovasc Imaging*. 2015;8:e002757.
17. Chen S, Zhang Q, Dai G, Hu J, Zhu C, Su L, Wu X. Association of depression with pre-diabetes, undiagnosed diabetes, and previously diagnosed diabetes: a meta-analysis. *Endocrine*. 2016;53:35–46.
18. Thuresson M, Jarlöv MB, Lindahl B, Svensson L, Zedigh C, Herlitz J. Symptoms and type of symptom onset in acute coronary syndrome in relation to ST elevation, sex, age, and a history of diabetes. *Am Heart J*. 2005;150:234–242.
19. Ångerud KH, Brulin C, Näslund U, Eliasson M. Patients with diabetes are not more likely to have atypical symptoms when seeking care of a first myocardial infarction. An analysis of 4028 patients in the Northern Sweden MONICA Study. *Diabet Med*. 2012;29:e82–e87.
20. Junghans C, Sekhri N, Zaman MJ, Hemingway H, Feder GS, Timmis A. Atypical chest pain in diabetic patients with suspected stable angina: impact on diagnosis and coronary outcomes. *Eur Heart J Qual Care Clin Outcomes*. 2015;1:37–43.
21. Lee DP, Fearon WF, Froelicher VF. Clinical utility of the exercise ECG in patients with diabetes and chest pain. *Chest*. 2001;119:1576–1581.
22. Rubler S, Gerber D, Reitano J, Chokshi V, Fisher VJ. Predictive value of clinical and exercise variables for detection of coronary artery disease in men with diabetes mellitus. *Am J Cardiol*. 1987;59:1310–1313.
23. Albers AR, Krichavsky MZ, Balady GJ. Stress testing in patients with diabetes mellitus: diagnostic and prognostic value. *Circulation*. 2006;113:583–592.
24. Kang X, Berman DS, Lewin H, Miranda R, Erel J, Friedman JD, Amanullah AM. Comparative ability of myocardial perfusion single-photon emission computed tomography to detect coronary artery disease in patients with and without diabetes mellitus. *Am Heart J*. 1999;137:949–957.
25. Paillole C, Ruiz J, Juliard JM, Leblanc H, Gourgon R, Passa P. Detection of coronary artery disease in diabetic patients. *Diabetologia*. 1995;38:726–731.
26. Patel NB, Balady GJ. Diagnostic and prognostic testing to evaluate coronary artery disease in patients with diabetes mellitus. *Rev Endocr Metab Disord*. 2010;11:11–20.
27. Cortigiani L, Bigi R, Sicari R, Landi P, Bovenzi F, Picano E. Prognostic value of pharmacological stress echocardiography in diabetic and nondiabetic patients with known or suspected coronary artery disease. *J Am Coll Cardiol*. 2006;47:605–610.
28. Elhendy A, van Domburg RT, Poldermans D, Bax JJ, Nierop PR, Geleijnse ML, Roelandt JR. Safety and feasibility of dobutamine-atropine stress echocardiography for the diagnosis of coronary artery disease in diabetic patients unable to perform an exercise stress test. *Diabetes Care*. 1998;21:1797–1802.

# **SUPPLEMENTAL MATERIAL**

**Table S1.** Severity of abnormal test results among patients with and without diabetes who have a positive non-invasive test.

	Diabetes N= 1908	Without diabetes N=7058
CTA positive (% of Total N undergoing CTA) <sup>#</sup>	N= 139 (14.85%, n=936)	N=395 (11.08%, n=3564)
Number of vessels with stenosis $\geq 70\%$ or left main $\geq 50\%$		
Single vessel	94 (67.63%)	296 (74.94%)
Double vessel	27 (19.42%)	72 (18.23%)
Triple vessel	15 (12.95%)	26 (6.83%)
ECG positive	N=7 (9.21%, n=76)	N= 47 (13.28%, n=354)
Nuclear scan positive <sup>^</sup>	N=126 (17.72%, n=711)	N=309 (13.12%, n=2355)
Number of coronary territories with inducible ischemia		
1	98 (77.78%)	251 (81.23%)
2	24 (19.05%)	51 (16.50%)
3	3 (2.38%)	6 (1.94%)
Echocardiogram positive	N=17 (9.19%, n= 185)	N=58 (7.39%, n=785)
Number of coronary territories with inducible ischemia		
1	12 (70.59%)	31 (53.45%)
2	3 (17.65%)	20 (34.48%)
3	2 (11.76%)	7 (12.07%)

CTA indicates computed tomographic angiography; ECG, electrocardiogram.

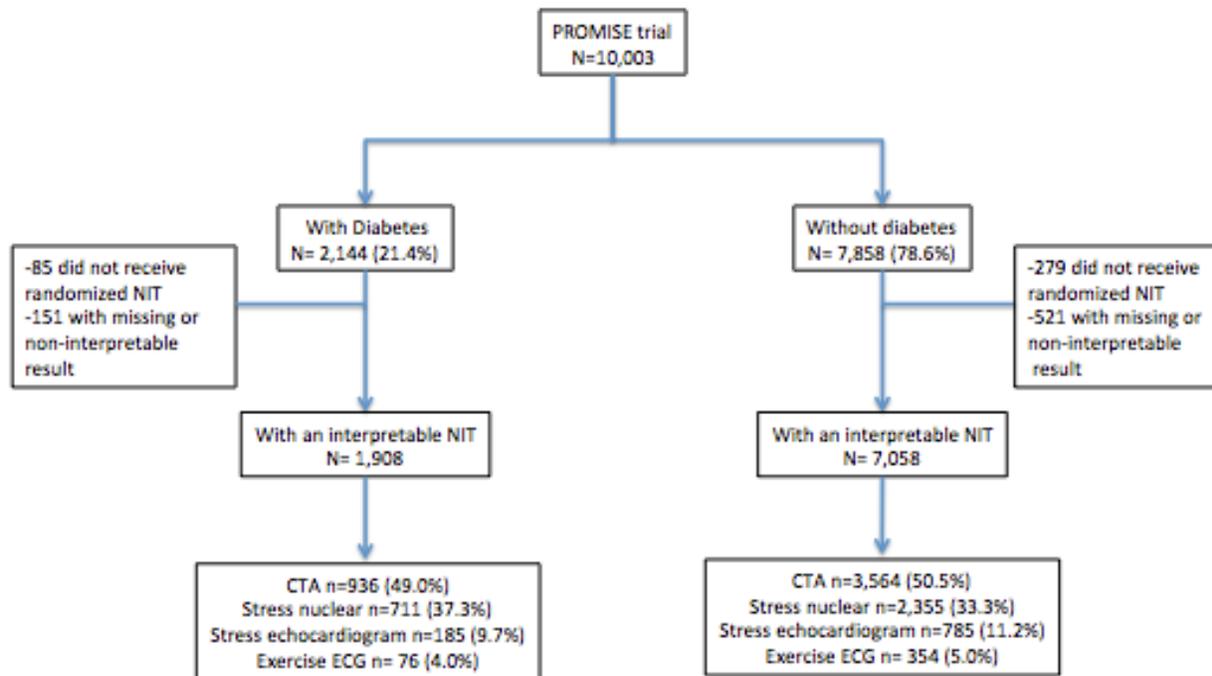
<sup>#</sup>3 patients with diabetes have disease in 4 vessels and 1 patient without diabetes has disease in 4 vessels; <sup>^</sup> 1 patient with diabetes positive due to treadmill result and 1 patient without diabetes positive due to treadmill result; \*Degree of ST depression not captured in case report form; †Test positivity included 1 patient in each group with an early positive ECG (< 3 min) but normal scan.

**Table S2.** Unadjusted clinical event rates by noninvasive test positivity and diabetes history.

<b>Clinical Endpoint/Subgroup</b>	<b>Unadjusted Clinical Event Rate (No. of Events/Sample Size)</b>	
	<b>Positive NIT</b>	<b>Negative NIT</b>
Death/MI/UAH		
Patients with diabetes	26/289 (9.00%)	49/1619 (3.03%)
Patients without diabetes	70/809 (8.65%)	120/6249 (1.92%)
Cardiovascular Death/MI		
Patients with diabetes	10/289 (3.46%)	25/1619 (1.54%)
Patients without diabetes	23/809 (2.84%)	72/6249 (1.15%)

MI indicates myocardial infarction; NIT, noninvasive test; UAH, unstable angina hospitalization.

**Figure S1.** Patient distribution.



Of the 10,003 enrolled patients, diabetic status was unknown in one.